

Editorial

# Post-COVID Syndrome— More Questions Than Answers

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Editorial accompanying the articles:

“Persisting Symptoms After COVID-19 – Prevalence and Risk Factors in a Population-Based Cohort”

„Post-acute Sequelae of Sars-Cov-2 Infection—Characterization of Community-Treated Patients in a Case—Control Study Based on Nationwide Claims Data“

„The Prevalence of Persistent Symptoms After COVID-19 Disease—a Cross-Sectional Study of 896 Patients Treated on an Outpatient Basis“

in this issue of *Deutsches Ärzteblatt International*

The incidence of newly diagnosed SARS-CoV-2 is declining and will continue on a downward trajectory over the coming weeks and months. Although the emergence of new virus variants and their impact on the course of the pandemic cannot be predicted, a laid-back spring and summer seem to be on the cards.

In this situation the consequences of the pandemic come to the fore. These include long COVID and the post-COVID syndrome. While the former refers to ongoing symptoms for more than 4 weeks after recovery from infection, the latter describes the continuing persistence of symptoms over 3 months later. I will focus on post-COVID syndrome because, as shown by an article in this issue of *Deutsches Ärzteblatt International*, in the majority of patients the symptoms recede within the first 3 months.

## Classification of persons with post-COVID symptoms

The experience from our clinic for persons with post-COVID symptoms shows that three groups of patients should be distinguished:

- Patients who were hospitalized due to COVID-19, with or without intensive care treatment.
- Patients who have a number of different symptoms, predominantly weariness and difficulty maintaining concentration (1–3), but do not experience major problems with daily tasks.
- Patients who are no longer able to pursue their normal lives, particularly due to massive exhaustion and inadequate resilience.

In this last group the symptoms resemble the well-known myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), observed following many infectious diseases, e.g., mononucleosis and cytomegaly (CMV infection), and also in the wake of autoimmune disorders such as sarcoidosis (4). No pathophysiologically satisfactory explanation for this disease has yet been put forward. Besides disorders of endothelial function, especially in the central nervous system, (auto)antibody-induced immunological processes and mitochondriopathies have been discussed as causes, alone or in combination. There exists as yet no established treatment for ME/CFS. The suggestions include immune apheresis and specific antibody therapies, but confirmatory studies are lacking. Given

the severe deleterious effects on the quality of life of patients with ME/CFS, further research is urgently required.

The first group, patients hospitalized for treatment of severe disease, are comparable with patients with long hospital stays for management of other serious illnesses, in that their symptoms are characterized by persisting breathing difficulties and low resilience. Lasting, usually fibrotic pulmonary residues and especially sarcopenia and critical illness neuropathy/myopathy have long been known and are explained as sequelae of the hyperinflammatory processes that are typical for severe COVID-19 (5, 6). Rather than the classic rehabilitation measures, these patients require a greatly intensified therapy program combining ergotherapy, physiotherapy, breathing therapy, and dietetics with structured stress training and neuro-cognitive training. Germany suffers from a shortage of specialized rehabilitation centers for these patients, and the infrastructure for outpatient measures to support the success achieved during inpatient rehabilitation is inadequate.

There remains the largest group: patients with ost-COVID. The studies published in this issue of *Deutsches Ärzteblatt International*, following up patients from a community medical center (2) or a hospital (1) or analyzing health insurance claims data (3), demonstrate the unspecific nature of the patients' symptoms. The most prominent manifestations are weariness and difficulty concentrating, together with the feeling of a lack of stamina. The study based on claims data included evaluation of a control group of patients with diseases other than COVID-19: patients who had suffered chronic illness before getting COVID-19 showed more post-COVID symptoms. The other two studies also found that the number of post-COVID symptoms increased with the number of pre-existing chronic illnesses.

The 2 years of the COVID-19 pandemic have greatly changed our lives and our attitude to life. Fear of the disease, the lockdown restrictions, and also the insecurity caused by frequently changing, often poorly explained COVID regulations have created a feeling of stress and malaise, and the prevalence of psychosomatic symptoms of illness has increased substantially (7). A study published in *JAMA Internal Medicine* concerned itself with persons who believed they had post-COVID but also ascertained whether

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prior COVID-19 could be confirmed by demonstration of antibodies (8). Astoundingly, persons without antibodies had even more symptoms than those in whom the disease could be shown: a sign of how strongly the pandemic is affecting even our feelings and perceptions.

### Differentiation is necessary

The challenge inherent in treating persons from the second group lies in differentiating between COVID-19-related medical conditions and pandemic-related psychosocial effects. To this end we need diagnostic instruments (9) to help us identify those persons with changes in immunological and cellular function (10) which explain their symptoms. Recent studies show that this appears to be less often the case in vaccinated patients (11). The Omicron variant, which produces a less pronounced inflammatory response, may also lead to less post-COVID. All data published so far, including the studies presented here, stem from the time when other variants predominated. As things stand, all we can offer these patients is multimodal symptom-oriented rehabilitation treatment.

Crucially, however, we will succeed in lessening the sequelae of COVID-19 only if we reduce the number of infections—chiefly by means of vaccination—and change our attitude towards the disease. The pathogen will not disappear in the foreseeable future: illness caused by SARS-CoV-2 will be just as much a feature of our lives as other infectious diseases. Even if the pathogen should become less virulent, as is now the case with Omicron, there will continue to be severe cases and deaths. Never in the history of mankind has there been a time when there were no pathogenic agents, and this will not change. We should take advantage of our means of prevention (vaccination and sensible distancing and hygiene measures, especially for those at greater risk) and the treatments that have already proven effective in order to learn to live with SARS-CoV-2.

#### Conflict of interest statement

The author declares that no conflict of interest exists

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